

## REMARKS

Claims 5-9, 11-14, 23-25, and 28-29 are pending.

### Claim Amendments

Applicants have canceled claims 8-9 and 26-27, have amended other claims to delete references to the cancelled claims, and have amended claim 24 to simplify and clarify the claimed subject matter. Applicants have also amended claim 24 to delete the term "magnetic particles." Applicants have added new claims 28 and 29 which correspond to cancelled claim 9.

### Telephone Interview

Applicants would like to thank the Examiner for conducting a telephone interview regarding this application on August 6, 2008. At the interview, all claims and the art of record were discussed. Also, at the interview, Applicants explained how the claims are non-obvious over WO 1999/31275 (Gold) in view of U.S. Patent 6,264,825 (Blackburn), consistent with what is set forth below.

### Sequence Compliance Objection

The Examiner alleges that the application fails to comply with 37 CFR §1.821(d) because the application discusses a sequence which is not set forth in the "Sequence Listing." Specifically, the Examiner points out Figures 1-4 as containing a nucleic acid sequence. Applicants respectfully traverse.

The application does not discuss any specific sequence listing. 37 CFR §1.821(d) provides that:

Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

However, neither the description nor claims of the instant application discusses any sequence that is set forth in the "Sequence Listing." Thus, 37 CFR §1.821(d) is inapplicable.

37 CFR §1.821 (c) provides that "[p]atent applications which contain disclosures of nucleotide and/or amino acid sequences" must contain the "Sequence Listing" section. However, the instant application does not contain disclosures of nucleotide and/or amino acid sequences for the purposes of 37 CFR §1.821(c). Figures 1-4 contain several nucleotide pairs solely for illustrative purposes to explain how the invention works. There is nothing unique about the depicted nucleotide pairs; in fact, they can be easily replaced with other examples of A-T or G-C nucleotide pairs. The precise nucleotide sequence is not important.

Accordingly, it is respectfully submitted that there is no disclosure of any nucleotide and/or amino acid sequences, and thus, there is no need for the application to contain the "Sequence Listing" section.

#### Objections to Drawings

The Examiner objects to Drawings because they contain more than 10 nucleotide pairs. Applicants respectfully request that this objection be held in abeyance until the application is allowed. Once the claims are allowed, Applicants will submit the replacement Drawings.

§103 obviousness rejection

Claims 5-9, 11-14, and 23-25 stand rejected under 35 U.S.C. §103 as allegedly being obvious over WO 1999/31275 (Gold) in view of U.S. Patent 6,264,825 (Blackburn). Applicants respectfully traverse the rejection.

The Examiner contends that it would have been obvious to combine the hairpin probes of Gold with the detection method of Blackburn. However, 1) the references should not be combined in the way the Examiner combines them; and 2) even if combined, the references do not render the invention obvious; especially in view of the amendments.

1. Gold and Blackburn are Improperly Combined

Gold is generally directed to nucleic acid ligand diagnostic biochips and methods for the detection of target molecules in test solutions. See, Gold, Abstract; Field of the Invention. Gold also discloses various methods to detect the binding of target molecules to nucleic acid ligands. See, Gold, Field of the Invention. Gold employs biochips, nucleic acid ligands, nucleic acid probes, and detection methods including fluorescence. Gold does not teach that a label selected from the group consisting of ceramic fine particles and semiconductors is attached to a loop-structured nucleic acid probe prior to hybridization.

Blackburn is generally directed to compositions and methods useful in acceleration of binding of target analytes to capture ligands on surfaces. See, Blackburn, Field of the Invention. Blackburn's invention lies in concentrating the target analyte in a detection chamber in which there is a detection electrode. See, Blackburn, col. 2, lines 14-19; and col. 93, lines 1-13. Blackburn teaches "a number of techniques that can be used to accelerate the rate of assay complex formation or increase the number of assay complexes in a given period of time,

wherein the target analyte becomes associated with a capture ligand on the electrode surface." See, Blackburn, col. 6, lines 61-66.

Blackburn's detection electrodes require the use of the so-called "self-assembled monolayer" which may include conductive oligomers. See, Blackburn, col. 24, lines 34-35; and col. 25, lines 1-2. Thus, Blackburn discloses a specific method of detecting a target analyte involving the concentration step and the self-assembled monolayer. Blackburn does not disclose or suggest pre-labeled loop-structured nucleic acid probes.

The Examiner picks some of the components of the Blackburn methods (an electron transfer moiety and some disclosed labels) and combines them with Gold to hold the claimed invention obvious. According to the Examiner, "it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the hairpin probes of Gold with detection methods of Blackburn, including Blackburn's metal (iron) and silicon containing labels." See, Office Action, at page 9. The Examiner provides the following reasons for combining Gold and Blackburn: a) Blackburn teaches that his method allows concentration of the target ligand with the capture ligand maximizing interaction; b) possibility to analyze very small samples; and c) more accurate and quantitative detection. *Id.*

However, the Examiner does not explain why a skilled artisan would select, for combination with Gold, certain Blackburn's components which are not central to Blackburn's invention while omitting the essential steps required in Blackburn, such as the concentration step and the self-assembled monolayer. While the Examiner states that the skilled artisan would have been motivated to combine Gold and Blackburn because of various advantages of Blackburn's methods, **this reasoning overlooks the fact that these advantages are due to Blackburn's methods as a whole.** The reasons provided by the Examiner are

not valid if the essential steps of Blackburn are omitted. In Blackburn, the ligand interaction is maximized and small samples can be detected precisely because of the concentration step and of the use of the self-assembled monolayer. If these steps are omitted, then there is no reason to expect that these effects would remain in place.

Applicants respectfully submit that combining Gold and Blackburn in the fashion the Examiner combines them is a result of improper hindsight, something that the Federal Circuit has repeatedly warned against. As the Federal Circuit stated:

As this court has stated, “virtually all [inventions] are combinations of old elements.” Therefore, an examiner [or accused infringer] may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner [or accused infringer] to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. *Yamanouchi Pharmaceutical Co., Ltd. v Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000).

KSR does not repeal the necessity to guard against hindsight. As the Federal Circuit stated, post-KSR, “...a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis...” *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

KSR does not stand for the proposition that one can selectively de-construct any references to find elements of the invention, and then combine the elements in the manner claimed by the invention to render the invention obvious. It remains that some reason must be identified to combine the elements in the manner claimed. As the Federal Circuit explained,

First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

As the Supreme Court stated:

...a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art...[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. (emphasis added). KSR, 127 S.Ct. 1727, 1741 (2007).

Thus, there must be some reason to combine Blackburn and Gold to arrive at the claims of the present invention. There is no such reason stated by the Examiner without resort to hindsight. It is tempting, but improper, to reconstruct the prior art, knowing what an applicant's invention is. It is also improper to omit essential steps required in Blackburn, pick several elements of Blackburn which are present in the claimed invention, and combine them with Gold to hold the invention obvious.

It is simply implausible that a skilled artisan would omit the key steps of Blackburn and pick and choose other parts of Blackburn's methods to arrive at the claimed invention. The methods of Gold and Blackburn are simply too different and too complex to know which parts of the methods would work with other methods; especially when some of the key steps of the methods are omitted. Moreover, neither Gold nor Blackburn teaches or suggests a key part of the present invention: attaching a label selected from the group consisting of ceramic fine particles and semiconductors to the loop-structured nucleic acid probe prior to hybridization.

Applicants respectfully submit that Blackburn and Gold should not be combined in the fashion the Examiner combines them.

**2. Even if Combined, Gold and Blackburn Do Not Render the Invention Obvious**

Even if Gold and Blackburn are combined in the way the Examiner proposes, they do not render the invention obvious.

While Gold generally discloses detecting target molecules using the biochip, it does not disclose or suggest: a) attaching a label to the loop-structured nucleic acid probe prior to hybridization; or b) selecting the label from the group consisting of ceramic fine particles and semiconductors. In addition, it does not disclose or suggest: detecting the probes on each electrode prior to the hybridization (as required by claim 7); detecting the double-chained complex by electronic methods (as required by claim 11); detecting the double-chained complex by electronic and magnetic methods (as required by claim 12); detecting the double-chained complex by electronic and optical methods (as required by claim 13); or detecting the double-chained complex by electronic, magnetic, and optical methods (as required by claim 14).

Blackburn does not cure the deficiencies of Gold.

Blackburn does not teach or suggest attaching a label to the loop-structured nucleic acid probe prior to hybridization, wherein the label is selected from the group consisting of ceramic fine particles and semiconductors. While Blackburn teaches the use of metal ions to connect the nucleic acids to the conductive oligomers as an internal control, Blackburn says nothing about the label being a ceramic fine particle or a semiconductor.

The attachment of the label to the nucleic acid probe is a key step of the claimed method. Since this step is not disclosed or suggested in Blackburn, the reference, even combined with Gold, does not render the invention obvious.

It would not have been obvious to the one of ordinary skill in the art that if some elements of Blackburn are combined with Gold's methods (which are primarily about detecting proteins, rather than nucleic acids), then the modified methods would work to detect nucleic acids, in the manner of the instant invention. It is improper hindsight to use the present invention as a blueprint to combine specific elements of Blackburn and Gold.

In summary, Applicants respectfully submit that the state of the art in this field is unpredictable and complex. The hypothetical person of ordinary skill in the art would not have been able to predict the effect of combining selected elements of the prior art methods, especially when the prior art methods significantly differ from each other, as Gold and Blackburn do. Even if combined, the references do not render the invention obvious because they do not teach or suggest an essential step: attaching a label to the loop-structured nucleic acid probe prior to hybridization, wherein the label is selected from the group consisting of ceramic fine particles and semiconductors.

Thus, there is not even a *prima facie* case of obviousness under these circumstances. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

### Conclusion

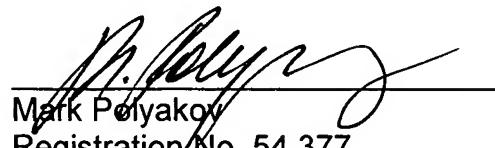
Applicants respectfully submit that all currently pending claims are patentable over the cited art. Accordingly, reconsideration of the rejection of claims and allowance of the case are requested.

Should the Examiner have any questions concerning the above, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any matters which the Examiner

believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

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